ECRONICON OPEN ACCESS

EC CARDIOLOGY
Review Article

Relationship between st2 and Myocardial Fibrosis in Heart Failure

Li Xiaodong[1] and Wang Wenyan[2]*

[1]*University of Electronic Science and Technology of China, Chengdu, China*

[2]*Sichuan Provincial People's Hospital Affiliated to University of Electronic Science and Technology of China, Chengdu, China*

***Corresponding Author:** Wang Wenyan, Heart Failure Center, Sichuan Provincial People's Hospital Affiliated to University of Electronic Science and Technology of China, Chengdu, China.

Received: August 08, 2019; **Published:** August 28, 2019

Abstract

Heart failure refers to the heart's systolic function and/or diastolic function disorder, the end stage of some type of cardiovascular disease. This article mainly refers to ST2 and its ligands IL-33, NT-pro BNP and other important factors. Has a good diagnostic and prognostic value for chronic heart failure.

Keywords: *Chronic Heart Failure; Acute Heart Failure; Myocardial Fibrosis; st2; il-33*

Introduction

ST2 and NT-pro BNP have a certain diagnostic value for acute heart failure and can better predict the occurrence of adverse cardiovascular events in AHF patients, especially death and readmission in heart failure. Continuous monitoring of ST2 concentration may be of greater value in predictions, and it is likely to play an important role in guiding treatment [1,2].

Overview of chronic heart failure and myocardial fibrosis

Chronic heart failure is a change in the structure and function of the heart caused by various factors, resulting in left ventricular group of clinical syndromes caused by a decrease in filling and ejection fraction in the final stage of development of various cardiovascular diseases and the leading cause of cardiovascular death. Chronic heart failure is a progressive disease. Once initiated, even if there is no new myocardial damage, the clinical stage is still consistent, and can continue to develop itself. According to relevant data, the mortality rate of chronic heart failure is as high as 50% and the increase in age leads to an increase in the prevalence of the disease. In the classification of chronic heart failure, most of the patients are classified according to the NYHA classification method, and the treatment can be improved by the classification of cardiac function. Therefore, the cardiac function classification method cannot represent the stage of the disease progression, and the disease prognosis cannot be determined.

Myocardial fibrosis refers to excessive deposition of collagen fibers in myocardial tissue, collagen concentration and collagen volume fraction increase significantly and the proportion of collagen in each type is disordered and unregulated. The pathological basis is the increase of myocardial tissue ratio in myocardial interstitium. The process of myocardial fibrosis and remodeling can cause abnormalities in myocardial function, metabolism and conduction, leading to heart failure and various cardiac diseases such as arrhythmia. Cardiovascular fibrosis can be observed in clinically common cardiovascular diseases such as hypertensive heart disease, ischemic cardiomyopathy, dilated heart disease, viral myocarditis, and diabetic cardiomyopathy. Therefore, myocardial fibrosis is inevitably accompanied by heart failure, and these two are accompanied by each other in the disease process. Ventricular remodeling is one of the main causes of heart failure, and one of the most important causes of ventricular remodeling is myocardial fibrosis. Myocardial fibrosis is the most important key pathological cause of heart failure. Accurate and timely diagnosis of myocardial fibrosis is the premise of treating heart failure. The myocardial fibrosis serum markers can accurately, quickly and conveniently determine the cause, development degree, therapeutic effect and prognosis of myocardial fibrosis [3].

In the relationship between the two, cardiac fibrosis is the result of fibrous connective tissue damage to the heart and occurs in all patients with heart failure. The heart undergoes abnormalities by injury or hemodynamics, from fibrotic gene phenotypes to pattern reconstruction of the heart structure, collagen fiber accumulation, markedly elevated concentrations, or changes in collagen composition. The mechanisms by which fibrosis promotes heart failure include increased stiffness in the ventricular wall and a decrease in the proportion of cardiomyocytes, leading to systolic dysfunction. Moreover, treatments for cardiac fibrosis include traditional anti-heart failure drugs such as ACEI, ARB and beta-blockers. Therefore, there is a close relationship between heart failure and myocardial fibrosis.

An overview of st2

ST2 (growth stimulation expressed gene 2) is a member of the interleukin-1 receptor family. The human ST2 gene is located on chromosome 2q12, about 40 kb and has four isoforms. There are two subtypes related to cardiovascular disease: Soluble form protein (sST2) and transmembrane form of protein (ST2L). ST2 was first reported by Japanese scholar Shinichi Tominaga in 1989. It is mainly involved in inflammation and immune processes in the body, but its ligand hasn't been found. So, it is considered to be an orphan receptor. In 2002, the Richard Lee team at Harvard Medical School reported ST2 expression is caused by myocardial stress and injury. Until 2005, when Schmitz., *et al*. discovered IL-33 as its functional ligand, the research on it gradually increased. ST2 is a receptor for IL-33, a cytokine similar to IL-1. It is secreted by living cells to cope with cell damage. IL-33/ST2 is present in cardiomyocytes and fibroblasts as a response to mechanical stimulation or injury. The experimental model shows that the interaction between IL-33 and the membrane receptor ST2L has obvious protective effects on the myocardium, especially preventing fibrosis and cardiomyocyte hypertrophy, reducing apoptosis, and having an overall improvement in cardiac function. Therefore, the IL-33/ST2L signal is a mechanically activated cardioprotective agent. The fibroblast-cardiomyocyte paracrine system may have a therapeutic effect on the regulation of myocardial overload and injury [4]. sST2 acts as a receptor capable of isolating IL-33, antagonizing the protective effect of IL-33/ST2L on the heart. In addition to its myocardial effects, the IL-33/ST2 system can play an additional role in its development and progression. ST2 is generally thought to be involved in the immune and inflammatory responses of the body. ST2L (transmembrane form ST2) is mostly expressed in mast cells and TH2 cells, while sST2 (soluble ST2) can be expressed in living cells. sST2 is mainly derived from cardiac fibroblasts and cardiomyocytes, and it participates in the development of cardiovascular diseases, having a strong prognostic value in them as well. When the body is exposed to risk factors such as pathogens, tissue damage or apoptosis, ST2L binds to IL-33, activates TH2 cells and releases related cytokines, producing an immune response. Therefore, ST2L is mainly dependent on TH2 cells. Related to inflammatory diseases such as asthma, pulmonary fibrosis, rheumatoid arthritis, sepsis, trauma, malignancy, helminth infection, ulcerative colitis [5]. Up-regulation of sST2 expression in cardiac pathology and blocking of IL-33 and ST2L after specific binding to IL-33 as a decoy receptor, results in a lack of adequate IL-33 protection in the myocardium, leading to myocardial remodeling and dysfunction [6]. sST2 is one of the most specific indicators for heart failure detection. It is almost independent of age, gender, BMI, heart failure, atrial fibrillation, anemia, and renal function. It has low biological variability and high stability. In addition, in the mouse model, knocking out the ST2 gene causes severe cardiomyocyte hypertrophy and cardiac interstitial fibrosis; blocking sST2 with antibodies greatly attenuates myocardial fibrosis and ventricular hypertrophy. Therefore, sST2 is closely related to myocardial fibrosis and ventricular remodeling [7,8].

st2 is related to heart failure

Heart failure is divided into acute heart failure and chronic heart failure. Acute heart failure has a high incidence and high mortality, which seriously threatens the health and quality of life of patients. Early detection, early diagnosis and early treatment are important measures to improve the patient's condition, reduce hospitalization time and reduce mortality. The soluble ST2 receptor (sST2) is a myocardial protein that is synthesized and secreted by the myocardial ST2 receptor gene by mechanical traction. The study confirmed that the change of sST2 level is a sensitive index reflecting myocardial fibrosis and ventricular remodeling. Studies have shown that sST2 can assess the severity and prognosis of AHF. Detecting sST2 levels in hospitalized and discharged patients with acute heart failure can be used for prognostic assessment. High concentrations of sST2 levels were positively correlated with sudden cardiogenic death rates within 1 year. When predicting the risk of death within 1 year, sST2 is superior to NT-pro BNP, but the combined detection of these two biomar-

kers can enhance the prognostic value. Rehman., *et al*. showed that the higher the sST2 concentration, the higher the mortality rate of AHF patients within one year, and the sST2 level was also closely related to cardiac function grading [9]. Frioes and other studies have shown that the sST2 concentration in patients with acute heart failure is positively correlated with a 6-month mortality or readmission rate [10]. This study shows that sST2 has the same value as BNP and the combined detection of the two markers may have a better prognostic value. Continuous monitoring of sST2 appears to increase its prognostic capacity. Bayes-Genis., *et al*. studied a small group of patients with acute heart failure and tested sST2 levels two weeks after discharge. The greater the decrease in sST2 levels within two weeks after discharge, the better the prognosis [11]. Another study examined sST2 levels in patients with heart failure within 48 hours of admission. Surviving patients had significantly different sST2 levels from the patients who died. Similarly, the percentage of sST2 decline can also predict long-term mortality. Compared with other biomarkers, sST2 has a lower biological variability rate and is more suitable for the assessment of heart failure, guiding treatment, and evaluating the prognosis of heart failure. The latest ACCF/AHA Heart Failure Guidelines and the 2014 China Heart Failure Diagnosis and Treatment Guidelines have introduced sST2 into biomarker recommendations. The latest edition of the American Heart Failure Guidelines recommends it as a biological marker that provides additional risk stratification values and landmarks. In the latest edition of the 2016 ESC Guidelines for Acute and Chronic Heart Failure, ST2 is also recommended as a Class IIa for risk stratification and prognosis assessment in patients with heart failure [12-14].

In patients with chronic heart failure, sST2 levels are significantly elevated, and the higher the level, worse is the cardiac function. Therefore, sST2 may be a new biomarker for the diagnosis of heart failure, and combined detection with NT-Pro BNP can improve the diagnostic value of heart failure. In the clinical application of sST2, serum sST2 was correlated with NT-pro BNP and left ventricular ejection fraction, which further confirmed that serum sST2 is closely related to the diagnostic value of chronic heart failure. sST2 is a secreted protein that can be detected in the blood, but there may be more than one source, and its biological half-life in the human body is still unclear. At the same time sST2 is not specific, so it cannot independently treat chronic heart failure. but it can be used as an important supplement to NT-pro BNP to improve the comprehensiveness of heart failure diagnosis [15].

sST2 is a powerful predictor of short-term mortality in patients with heart failure and can increase the predictive value of other indicators in heart failure, and sST2 is a significant pathophysiological process in heart disease and is not affected by age and renal function. It is: 1) A strong prognosis for short-term and long-term outcomes; 2) Predicting the risk of major adverse cardiovascular events, primarily heart failure-related events; 3) Demonstrating added value to clinical and other biomarkers. When ST2 > 35 ng/ml in patients with acute decompensated heart failure, the risk of death and hospitalization for heart failure was significantly increased. Serum sST2 concentrations strongly predict mortality within 1 year in patients with acute heart failure and in those without heart failure. In studies of patients with acute heart failure, sST2 is again the first choice for predicting 1-month and 1-year mortality predictions; and exhibits higher predictive value than other biomarkers, such as NT-proBNP, BNP, CRP or troponin, NT-pro BNP is an endocrine hormone synthesized and secreted by atrial and ventricular myocytes. It is closely related to atrial and ventricular volume, ventricular remodeling, etc. It is an important biochemical marker reflecting ventricular dysfunction. Studies have shown that early detection of NT- Pro BNP can assist in the clinical diagnosis of acute heart failure and prognosis. The combination of sST2 and NT-pro BNP can be better used for the diagnosis, risk stratification and prognosis assessment of heart failure. In a related literature, Ahmad., *et al*. observed 813 patients with systolic heart failure in an emergency department and found that sST2 is a strong independent predictor of pump failure and sudden cardiac death [16]. Zilinski., *et al*. observed that patients admitted to the ICU in advanced ICU heart failure treated with pulmonary catheter guidance, elevated sST2 within 48 hours independently predicted a 90-day prognosis [17]. In another document, Zhang., *et al*. found that sST2 is a strong independent marker of hospitalized patients with heart failure in a follow-up of 19.8 months of hospitalization of 1528 heart failure patients with all-cause death and heart transplantation as a negative event. Predictors can significantly increase the value of NT-pro BNP in risk prediction; because of molecular mechanisms, sST2 protein has a higher diagnostic value in idiopathic dilated cardiomyopathy than ischemic myocardium in chronic heart failure disease [18].

The relationship between st2 or il-33 and myocardial fibrosis

Myocardial fibrosis, also known as myocardial calcification, is caused by moderate to severe coronary atherosclerotic stenosis causing myocardial fiber persistence and/or recurrence myocardial ischemia. The result of hypoxia leads to ischemic heart disease that gradually develops into heart failure, namely chronic ischemic heart disease [19].

In 2007, Sanada., *et al*. first recorded that IL-33 prevents cardiomyocyte apoptosis, reduces infarct size, fibrosis and apoptosis and improves myocardial infarction by inducing anti-apoptotic proteins after ischemia-reperfusion in rats. Heart function and survival rate [20]. IL-33 is associated with the expression kinetics of anti-apoptotic gene B-cell lymphoma 2 (Bcl-2), which is consistent with its anti-apoptotic effect. Since then, several experimental studies have also shown that IL-33 attenuates myocardial fibrosis induced by increased cardiovascular load, indicating that IL-33 directly inhibits the profibrotic activity of cardiac fibroblasts. Treatment of rat cardiac fibroblasts with IL-33 was also found to impair the migration activity of fibroblasts or their precursors affecting the myocardium. IL-33 levels were found to be significantly elevated in cardiomyocytes extended by cardiopulmonary bypass, and administration of IL-33 was shown to inhibit myocyte amino acid incorporation and growth, thereby preventing cardiac hypertrophy. IL-33 protects cardiomyocytes from hypoxia-induced apoptosis *in vitro*, which is partially inhibited by sST2, highlighting the key role of IL-33 in regulating cardiomyocyte function and its protection in cardiac fibrotic diseases.

Effects [21]

sST2 disrupts the cardioprotective effects of IL-33 by isolating its availability for binding to the transmembrane receptor ST2L. Both cardiac fibroblasts and cardiomyocytes express IL-33 and sST2 and the expression levels increase with the response of myocardial stress. From a clinical point of view, this problem is supported because of the high concentration of sST2 in patients with acute myocardial infarction and acute heart failure, and with infarct amplitude, cardiac insufficiency, hemodynamic damage, and neurohormonal disorders.

Parameter related

Based on the above, sST2 is considered to be a biomarker for poor prognosis in patients with cardiovascular disease [22]. In addition, cardiogenic shock and increased C-reactive protein levels are associated with higher sST2 levels. Studies have shown that whether it is acute heart failure or chronic heart failure, higher the level of sST2, more severe the myocardial fibrosis, and higher the severity of heart failure. The PRIDE (Emergency Department Breathing Pro-BNP Study) study highlights the potential use of sST2 in acute heart failure. This study shows that sST2 can predict 30-day mortality in patients with acute heart failure. High-risk patients can be identified by detecting ST2 within the first 30 days after acute onset, with a predicted value of more than one year. Since then, some studies have subsequently highlighted its use as a diagnostic and prognostic tool. Weir., *et al*. showed that sST2 can predict functional recovery and left ventricular remodeling during post-infarction. The level of sST2 was positively correlated with the degree of cardiac fibrosis. Along these directions, the recent observation of the left ventricular assist device (LVAD) resulted in a significant decrease in sST2 levels and normalization within 3 months after implantation, thereby attenuating cardiac fibrosis and inflammation [23].

Conclusion and Shortcomings

In view of the fact that ST2 is less affected by traditional factors, many studies have found that the predicted value of ST2 changes in patients with heart failure is greater than the ST2 level at baseline, which requires further research support. In the range of reference values of ST2 in healthy people, in view of the lack of previous studies and small sample size, further exploration may be needed. A small number of studies have found that changes in ST2 concentration are related to standard drug therapy for heart failure, whether ST2 concentration changes can provide guidance for the treatment of heart failure, or use ST2 concentration changes in combination with other clinical factors to assess whether the patient's cardiac function is more effective, and whether drugs or other methods can be invented to reduce IL-level by reducing sST2 levels in the blood circulation. Combination of IL-33 to reduce myocardial repair is a direction we can consider. Of course, the deeper relationship between sST2 and IL-33 requires further research. Moreover, the myocardial remodeling process often has no obvious clinical symptoms, and it is difficult to determine the time when remodeling begins. Reconstruction cannot be found

without imaging techniques such as echocardiography, which calls for the use of biological markers to discover myocardial remodeling. The pathological process has become very attractive. Considering the importance of early myocardial remodeling in heart failure, it is more meaningful to further explore the role of sST2 in the assessment of future heart failure in high-risk populations [24].

Bibliography

1. Sun RR., *et al*. "Biomarkers and heart disease". *European Review for Medical and Pharmacological Sciences* 18.19 (2014): 2927-2935.
2. Huang Jing., *et al*. "New progress in st2 in cardiovascular disease research". *Chinese Medical Innovation* 13.25 (2016): 87-89.
3. Li Lifeng and Zhu Mingjun. "Professor Zhu Mingjun's experience in the treatment of chronic heart failure". *World Journal of Integrated Traditional Chinese and Western Medicine* 5.4 (2010): 291-294.
4. Demyanets S., *et al*. "Components of the interleukin-33/ST2 system are differentially expressed and regulated in human cardiac cells and in cells of the cardiac vasculartur". *Journal of Molecular and Cellular Cardiology* 60 (2013): 16-26.
5. Cao Mengyuan and Xu Yongni. "Research progress of il-33/st2 signaling pathway in diseases". *Advances in Microbiology and Immunology* 41.6 (2013): 71-75.
6. Seki K., *et al*. "Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling". *Circulation: Heart Failure* 2.6 (2009): 684-691.
7. Xu Yamei and Ge Junbo. "Biological characteristics and clinical significance of a novel heart failure marker sST2". *Chinese Journal of Laboratory Medicine* 38.7 (2015): 498-501.
8. Januzzi J., *et al*. "ST2 and prognosis in acutely decompensated heart failure: the International ST2 Consensus Panel". *American Journal of Cardiology* 115.7 (2015): 26B-31B.
9. Rehman SU., *et al*. "Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure". *Journal of the American College of Cardiology* 52.18 (2008): 1458-1465.
10. Frioes F., *et al*. "Prognostic value of s ST2 added to BNP in acute heart failure with preserved or reduced ejection fraction". *Clinical Research in Cardiology* 104.6 (2015): 491-499.
11. Bayes GA., *et al*. "Soluble ST2 monitoring provides additional risk stratification for outpatients with decompensated heart failure". *Revista Española de Cardiología* 63.10 (2010): 1171-1178.
12. Zhai Yuqing and Peng Daoquan. "Diagnostic value of soluble st2 in patients with chronic heart failure". *Chinese Journal of Cardiology* 18.5 (2013): 334-338.
13. Maisel A., *et al*. "Serial ST2 testing in hospitalized patients with acute heart failure". *American Journal of Cardiology* 115.7 (2015): 32B-37B.
14. For diagnosis TTF and Acute T O. "2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary A Report of the American College of Cardiology".
15. Dai Qian., *et al*. "Evaluation of the performance of soluble st2 and its diagnostic value in patients with heart failure". *Chinese Journal of Laboratory Medicine* 37.5 (2014): 394-398.
16. Ahmad T., *et al*. "Biomarkers of myocardial stress and fibrosis as predictors of mode of death in patients with chronic heart failure". *Heart Failure* 2.3 (2014): 260-268.
17. Zilinski JL., *et al*. "Measurement of multiple biomarkers in advanced stage heart failure patients treated with pulmonary artery catheter guided therapy". *Critical Care* 16.4 (2012): R135.
18. Zhang RC., *et al*. "The prognostic value of plasma soluble ST2 in hospitalized chinese patients with heart failure". *PLoS One* 9.10 (2014): e110976.

19. Demyanets S., *et al*. "Soluble ST2 and Interleukin-33 levels in coronary artery disease: relation to disease activity and adverse outcome". *PLoS One* 9.4 (2014): e95055.

20. Sanada S., *et al*. "IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system". *Journal of Clinical Investigation* 117.6 (2007): 1538-1549.

21. Miller AM., *et al*. "IL-33 reduces the development of atherosclerosis". *Journal of Experimental Medicine* 205.2 (2008): 339-346.

22. Zhang K., *et al*. "Predicting value of serum soluble ST2 and interleukin-33 for risk stratification and prognosis in patients with acute myocardial infarction". *Chinese Medicine* 126.19 (2013): 3628-3631.

23. Weir RA., *et al*. "Serum Soluble ST2 A potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction". *JACC: Journal of the American College of Cardiology* 55.3 (2010): 243-250.

24. Breidthardt T., *et al*. "Heart failure therapy-induced early ST2 changes may offer longterm therapy guidance". *Journal of Cardiac Failure* 19.12 (2013): 821-828.

Volume 6 Issue 9 September 2019